

## EDITORIAL COMMENT

### Renal Artery Stenosis: Searching for the Algorithms for Diagnosis and Treatment\*

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The study by Gowda et al. (1) in this issue of the *Journal* challenges the “legitimacy” of angiography as the gold standard for the diagnosis of renal artery stenosis due to fibromuscular dysplasia (FMD). It reinforces the dilemma caused by the limited evidence-based approach to the diagnosis and treatment of renal artery stenosis regardless of etiology. Though there is a general consensus that percutaneous transluminal angioplasty is the procedure of choice for FMD and is both safe and effective, the evidence for this is dated, largely descriptive, and reported in the prestant era. For the much more common setting of atherosclerotic renal artery stenosis, a few widely quoted randomized comparative trials with serious flaws in study design, execution, and interpretation have led to the conventional wisdom by many that renal revascularization is ineffective (an opinion we do not share). When compared to other areas of endovascular intervention, the evidence base in this field is quite inferior.

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For the present, the decision to pursue percutaneous therapy is based on descriptive single-center series, multi-center registries, and some largely anecdotal reports suggesting that percutaneous revascularization decreases the need for antihypertensive medication, cures hypertension in a small minority, and slows the progression to renal failure in atherosclerotic renal artery disease (2–4). The superiority of endovascular therapy over medical therapy has not been shown (5–7). The evidence for intervention in FMD is somewhat more compelling (8–11), but the incidence of fibromuscular disease is quite low, likely only 1/10th as common as atherosclerotic renal artery stenosis. Fibromuscular dysplasia of the renal arteries accounts for <1% of the hypertensive population; therefore, it is an uncommon clinical scenario in clinical practice (12).

Algorithms for screening for renal artery stenosis are also debated, with a wide range of techniques available including duplex ultrasonography, contrast-enhanced magnetic reso-

nance arteriography (MRA), three-dimensional computed tomography (CT), and selective or nonselective contrast angiography (13). Because of lower accuracy, nuclear renal-flow scanning and plasma renin assays, both with or without angiotensin-converting enzyme inhibitor stimulation, are less commonly employed (14). Angiography has remained the gold standard in most studies.

## EVIDENCE BASE TO DATE

Only a few randomized trials to date have examined the efficacy of percutaneous revascularization compared with medical therapy or surgery, each with significant design, enrollment, or data analysis problems (Table 1). Four such studies have been reported in the literature (5–7,15), three in comparison with medical therapy and one with surgical revascularization. A recent meta-analysis of the three medical therapy versus balloon angioplasty studies (5–7) found only a small, although significant reduction in blood pressure in patients undergoing intervention (16). These studies have at least some faults in common: stents were rarely used although they have become the de facto standard for percutaneous endovascular intervention in atherosclerotic renal artery stenosis (3); some or all of the interventionists lacked experience; the studies were underpowered; substantial crossover occurred; and there were significant design and enrollment problems.

Particular criticism has been leveled at the largest of these studies, from the Dutch Renal Artery Stenosis Intervention Cooperative Study Group (5), which concluded that “In the treatment of patients with hypertension and renal-artery stenosis, angioplasty has little advantage over antihypertensive-drug therapy.” This widely quoted study had several egregious issues. One hundred six patients were enrolled at 26 sites, thus averaging only two angioplasty patients per site over a six-year period. The investigators’ results do not demonstrate efficacy of endovascular therapy as reported by researchers with extensive experience and expertise. Several other factors may have contributed to a Type II error: nearly half the medical therapy cohort underwent angioplasty after the first three months because of failure to control blood pressure on medication or decreased renal function; a significant percentage of the patients had less than critical stenosis (10% had <50% stenosis, an unspecified number had <60%); and the end point was one year, a time frame at which many patients undergoing balloon angioplasty would have sustained restenosis (the three-month results were more favorable). Stenting likely would have had substantially better results.

Although there is extensive nonrandomized evidence that stenting is superior to balloon angioplasty (17), only one published study has compared balloon angioplasty with stenting (18), although the latter has become the standard of care. In that study, restenosis was 48% with balloon angioplasty versus 14% with stenting at six months; acute success

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**Table 1.** Randomized Trials in Renal Artery Stenosis Intervention

|                   | Year | n   | Medical | Balloon | Stent | Surgery | End Points                |
|-------------------|------|-----|---------|---------|-------|---------|---------------------------|
| Weibull (15)      | 1993 | 58  |         | X       |       | X       | BP/renal function         |
| Plouin (7)        | 1998 | 49  | X       | X       |       |         | BP                        |
| Webster (6)*      | 1998 | 55  | X       | X       |       |         | BP/renal function         |
| van de Ven (17)   | 1999 | 84  |         | X       | X     |         | Patency/BP/renal function |
| van Jaarsveld (5) | 2000 | 106 | X       | X       |       |         | BP/renal function         |

\*Five patients underwent nephrectomy or bypass surgery in lieu of angioplasty.  
BP = blood pressure.

was only 57% with balloon angioplasty versus 88% with stenting. In comparing medical therapy and stenting, the clinician is left without randomized clinical data. There remain conservative physicians who suggest that stenting should be reserved as a bail-out procedure, but it is our opinion that this approach is difficult to justify (19).

## STUDY DESIGN AND PATIENT ENROLLMENT

The premise of the study by Gowda et al. (1), along with their methods and conclusions, raises potential concerns. A small number of patients with abnormal color flow duplex imaging (CFDI) underwent intravascular ultrasound (IVUS) and renal angiography. It is unclear how many patients were screened during the 28-month period, how many had abnormal renal artery duplex ultrasound examinations that were not suggestive of FMD, or how the criteria for noninvasive diagnosis of FMD utilizing duplex ultrasonography were derived. The mean age of 62 years (including an 86-year-old) is rather remarkable for a disease primarily occurring in young women (20). Whereas various criteria have been proposed for invasive screening (21), it is unclear whether these patients met the criteria.

**Noninvasive assessment.** The investigators (1) claim that 100% of screened patients had successful completion of diagnostic studies despite performing ultrasound in the supine position only. The vast majority of renal arteries (particularly the mid and distal vessels) cannot be fully imaged with the patient supine (22), thus requiring placing the patient in the lateral decubitus position. The technique of duplex ultrasonography of the renal arteries is “time-consuming, technically demanding and has a steep learning curve” (23). We continue to experience an approximately 10% failure rate for a complete examination of both renal arteries (full visualization from the ostium to the hilum of the kidney). This is in keeping with the residual failure rate of duplex ultrasonography of up to 20% reported in laboratories with highly experienced personnel (24,25). Although Gowda et al. (1) claim that improved techniques mitigate the presence of bowel gas and obesity, those factors as well as difficulties inherent in imaging small vessels, the posterior location of the mid and distal arteries, inability of patients to hold their breath, and simply being unable to obtain a good acoustic window remain unresolved problems. Use of ultrasound contrast and improved technology will likely reduce the failure rate in the future.

Gowda et al. (1) have introduced criteria for ultrasound

detection of FMD including a renal:aortic systolic flow velocity ratio  $\geq 2.0$  and “abnormal, non-laminar flow patterns (such as aliasing and spiraling flow)” that do not have the weight of known methodology or published literature. The flow velocity ratio used by the investigators is at variance with the accepted standard of  $\geq 3.5$ . A ratio of  $\geq 2.0$  has limited specificity and would have included the majority of patients without significant stenosis in prior studies (23). In fact, only 10 of the 32 renal arteries said to have FMD demonstrated higher systolic velocity ratios, and we do not know what the correlation of these vessels was with angiography. The flow pattern description is also unfamiliar, and we are not aware of any such criteria in the published reports. “Aliasing” is not related to laminar flow, but rather to the pulse repetition frequency of a particular Doppler waveform, whereas “spiraling” is a low-specificity descriptive feature and not a term commonly associated with duplex imaging. It is not clear whether all these criteria were prospectively evaluated and validated.

As with the definition of duplex criteria for FMD, the definition of IVUS findings consistent with this disease appears ad hoc; we are unaware of established criteria with appropriate correlation with pathological findings. Because the IVUS findings are being used as confirmatory of the CFDI observations, this further raises questions regarding the interpretation of the investigators’ data. At the same time, Gowda et al. (1) state that “in some patients whose contralateral renal arteries were normal or borderline and whose CFDI was normal, IVUS was performed and was uniformly normal.” Not having been told how many patients or arteries this represented, it is hard to know how much emphasis to place on “uniformity” or even how to interpret this finding.

**Angiographic evaluation.** The angiographic evaluation of these patients may have been marred by a number of factors. First, the three cardiologists reviewed the angiograms for “the classic beaded appearance” of FMD, although this is seen in only approximately 75% of cases (12); there are five distinct types of FMD, and failure to screen for the others may have resulted in false negatives. The choice of a “10–20° right anterior oblique projection for the right renal artery . . . to view the ostium clearly” was not ideal in that it maximizes foreshortening and actually minimizes the odds of complete visualization, given that the artery courses 30° ventrally from its origin at the aorta (26). In addition, the ostium is not the area of primary interest for FMD,

although it is for atherosclerosis (27). Second, the investigators state that it "should not be surprising" that there was failure to detect by angiography the "very short, planar, cleft-like lesions [that] can escape detection in all but one optimal view." This may well have been due to their view selection. Third, by using selective angiography, the investigators likely missed accessory renal arteries (estimated to occur in about 20% of patients (28) that may originate anywhere from the lateral aorta to the iliac arteries, that may arise at steep angulations up to 90° from their origin, may be difficult to interrogate using appropriate Doppler angles, may be quite small, occur in groups of three or more, and be difficult to detect by ultrasound.

The study by Leung et al. (25), which enrolled hypertensive patients and obtained duplex, MRA, and angiography of 85 renal arteries, using angiography as the gold standard is of questionable applicability, given that only 5 of the 45 abnormal arteries had FMD. It should be noted that duplex ultrasonography resulted in seven false positive and seven false negative readings. With regard to the conclusion by Beregi et al. (29) suggesting that renal angiography with pressure measurements should be the gold standard, it is our observation in FMD (unlike with atherosclerotic disease) that translesional pressure measurements are unreliable markers of severity of obstruction. There is no published evidence that "hydraulic assessment is a better predictor (than percent stenosis by arteriography) of response to revascularization" in FMD.

Based on the small number of patients, the problems inherent in the screening process, and the technique issues raised by the methodologies used with each of the measurement end points, we do not believe that a compelling case can be made for abandoning renal angiography as the gold standard. We also cannot recommend abandoning arteriographic criteria and using balloon angioplasty in angiographically normal-appearing arteries based on the data presented. Furthermore, we would be very cautious about accepting the diagnosis of fibromuscular dysplasia and oversizing noncompliant balloons in the renal arteries of elderly patients as described by Gowda et al. (1). We maintain that the appropriate algorithm for the diagnosis of fibromuscular dysplasia of the renal arteries remains a high clinical index of suspicion, a potentially abnormal renal artery duplex ultrasound, CT angiogram or MRA study, and a confirmatory contrast arteriogram.

## THE FUTURE

Various unpublished initiatives are under way to provide an evidence base. The ASPIRE trials (Action on Secondary Prevention through Intervention to Reduce Events) enrolled patients who underwent stenting after suboptimal balloon angioplasty; this was a nonrandomized safety and efficacy study. Preliminary data on 208 patients presented at the 2002 American Heart Association Scientific Sessions revealed a 16.8% nine-month restenosis rate (30). A trial in

the planning stage, CORAL (Cardiovascular Outcome in Renal Atherosclerotic Lesions), is designed to compare medical therapy versus medical therapy plus stenting. RESIST (Randomized Comparison of Safety and Efficacy of Renal Stenting) is an ongoing trial comparing renal stenting with or without distal protection and with or without glycoprotein IIb/IIIa inhibition to assess renal function. The design problems facing these studies are substantial, including the need for a sensitive end point to assess the affect of intervention on the kidney. In an attempt to provide a level playing field with well-designed enrollment criteria, study populations, and outcomes reporting, a consortium of American Heart Association councils and the Society of Interventional Radiology FDA Device Forum Committee have published guidelines for future trials (31). Until there is clarity provided by these trials, the clinician will be forced to continue practice based upon existing standards, waiting for evidence to support the therapeutic alternatives.

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